PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): Brian J. Balin et al.

Serial No: 09/227,749 Group Art Unit: 1623

Filed: January 8, 1999 Examiner: Elli Peselev

Att. Docket No.: I1059/20001 Confirmation No.: 7756

For: TREATMENT AND DIAGNOSIS OF ALZHEIMER'S DISEASE

DECLARATION OF DR. BRIAN J. BALIN UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Brian J. Balin, hereby declare that:

1. I am a named inventor of U.S. Patent Application 09/227,749 filed January 8, 1999 and U.S. Provisional Application 60/070,855, filed on January 9, 1998.

2. I have been a professor of Pathology, Microbiology and Immunology at the Philadelphia College of Osteopathic Medicine in Philadephia, Pennsylvania since 1999.

3. I am also Director, Basic Science Research Center for Chronic Disorders of Aging at the Philadelphia College of Osteopathic Medicine.

4. I am on the editorial board for the Association of Clinical Scientists.

5. I have served on NIH grant review panels.

6. I received my PhD in Experimental Pathology in 1987 from the University of Maryland School of Medicine in Baltimore, MD.

7. I have worked directly on Alzheimer's Disease research since 1989 and in neuropathology generally since September, 1981.

8. Attached as Exhibit A is a list of scientific articles for which I was a co-author and which deal directly with an aspect of Alzheimer's disease.

9. Attached as Exhibit B is a list of additional scientific articles for which I was a co-author and which deal with neuropathology.

10. To my knowledge, during the period, December 21, 1981 through December 6, 1983, tetracycline was not recognized to have beneficial effects in Alzheimer's Disease.

11. To my knowledge, during the period, December 7, 1983 until the dates of the inventions by the applicants claimed in the present application serial number 09/227,749, tetracycline was not recognized to have beneficial effects in Alzheimer's Disease.

12. Consistent with my statements in Paragraphs 10 and 11 is the fact that a search of the PubMed database of the National Center for Biotechnology Information of the U.S. National Library of Medicine, performed on or about October 26, 2006, and using search terms to uncover database records containing both of the terms, "alzheimer" and "tetracycline", did not reveal any abstracts or titles linking tetracycline to an effect on Alzheimer's disease.

13. The PubMed database was capable of finding articles as early as 1980 as indicated by the fact that the earliest record found was a 1980 article (identifying the use of the fluorescent probe chlortetracycline to detect diamagnetic cations.)

14. Consistent with my statements in Paragraphs 10 and 11 is attached Exhibit C, are excerpts from the "Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias of Late Life", which was originally published in May 1997 by the

Application No. 09/227,749
Rule 132 Declaration
Attachment to Reply to Office Action of May 9, 2005

American Psychiatric Association.

15. I further declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 11/08/05

Brian J. Balin

Attachments: Exhibits A, B and C

EXHIBIT A

(Declaration of Dr. Brian J. Balin Under 37 CFR 1.132)

PUBLICATIONS DIRECTLY RELATED TO ALZHEIMER'S DISEASE

Little, C.S., Bowe, A., Lin, R., Litsky, J., Balin, B.J., and Fresa-Dillon, K.L.:Age alterations in extent and severity of experimental intranasal infection by *Chlamydophila pneumoniae* in BALB/c mice. **Infect. and Immun. 73:**1-12, 2005

Balin, B.J., Hammond, C.J., Little, C.S, MacIntyre, A., Appelt, D.M.: *Chlamydia pneumoniae* in the Pathogenesis of Alzheimer's disease. In:**Chlamydia pneumoniae Infection and Diseases.** Kluwer Academic/Plenum Publishers, New York, New York; edited by Drs. M. Bendinelli, Y. Yamamoto, and H. Friedman, 2004, pp. 211-226.

Itzhaki RF, Wozniak MA, Appelt DM, Balin BJ. Infiltration of the brain by pathogens causes Alzheimer's disease. **Neurobiol Aging.** 2004 May-Jun;25(5):619-27. Review.

Little CS, Hammond CJ, MacIntyre A, Balin BJ, Appelt DM. Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice.Neurobiol Aging. 2004 Apr;25(4):419-29.

MacIntyre A, Abramov R, Hammond CJ, Hudson AP, Arking EJ, Little CS, Appelt DM, Balin BJ. Chlamydia pneumoniae infection promotes the transmigration of monocytes through human brain endothelial cells. **J Neurosci Res.** 2003 Mar 1;71(5):740-50.

Balin, B.J., Appelt, D.M., Whittum-Hudson, J.A., Hudson, A.P.: Infectious Agents and Alzheimer's Disease. **Recent Research Developments in Molecular and Cellular Biochemistry 1**:187-202, 2003.

MacIntyre, A., Hammond, C.J., Little, C.S., Appelt, D.M., Balin, B.J.: *Chlamydia pneumoniae* infection alters the junctional complex proteins of human brain microvascular endothelial cells. **FEMS Microbiology Letters 217**: 167-172, 2002.

Balin BJ, Appelt DM. Role of infection in Alzheimer's disease. **J Am Osteopath Assoc.** 2001 Dec;101(12 Suppl Pt 1):S1-6. Review.

Hudson, A.P., Gerard, H.C., Whittum-Hudson, J.A., Appelt, D.M., Balin, B.J.: *Chlamydia pneumoniae*, APOE genotype, and Alzheimer's Disease. In:***Chlamydia pneumoniae* and Chronic Diseases**, pp 121-136, 2000; Springer-Verlag, Berlin, Germany; edited by Johanna L'Age-Stehr).

Arking, E.J., Appelt, D.M., Abrams, J.T., Kolby, S.J., Hudson, A.P., and Balin, B.J.: Ultrastructural Analysis of *Chlamydia pneumoniae* in the Alzheimer's brain.

Pathogenesis 1(3):210-211, 1999.

Balin BJ, Loewy AG, Appelt DM. Analysis of transglutaminase-catalyzed isopeptide bonds in paired helical filaments and neurofibrillary tangles from Alzheimer's disease. **Methods Enzymol.** 1999;309:172-86.

Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. **Med Microbiol Immunol (Berl).** 1998 Jun;187(1):23-42.

Appelt DM, Balin BJ. The association of tissue transglutaminase with human recombinant tau results in the formation of insoluble filamentous structures. **Brain Res.** 1997 Jan 16;745(1-2):21-31.

Appelt DM, Kopen GC, Boyne LJ, Balin BJ. Localization of transglutaminase in hippocampal neurons: implications for Alzheimer's disease. **J Histochem Cytochem.** 1996 Dec;44(12):1421-7.

Appelt DM, Balin BJ. Analysis of paired helical filaments (PHFs) found in Alzheimer's disease using freeze-drying/rotary shadowing. **J Struct Biol.** 1993 Sep-Oct;111(2):85-95.

Lee VM, Balin BJ, Otvos L Jr, Trojanowski JQ. A68: a major subunit of paired helical filaments and derivatized forms of normal Tau. **Science.** 1991 Feb 8;251(4994):675-8.

EXHIBIT B

(Declaration of Dr. Brian J. Balin Under 37 CFR 1.132)

PUBLICATIONS RELATED TO NEUROPATHOLOGY GENERALLY

Reed LA, Schmidt ML, Wszolek ZK, Balin BJ, Soontornniyomkij V, Lee VM, Trojanowski JQ, Schelper RL. The neuropathology of a chromosome 17-linked autosomal dominant parkinsonism and dementia ("pallido-ponto-nigral degeneration"). **J Neuropathol Exp Neurol.** 1998 Jun;57(6):588-601.

Katsetos CD, Herman MM, Balin BJ, Vinores SA, Hessler RB, Arking EJ, Karkavelas G, Frankfurter A. Class III beta-tubulin isotype (beta III) in the adrenal medulla: III. Differential expression of neuronal and glial antigens identifies two distinct populations of neuronal and glial-like (sustentacular) cells in the PC12 rat pheochromocytoma cell line maintained in a Gelfoam matrix system. **Anat Rec.** 1998 Mar;250(3):351-65.

Lieberman AP, Trojanowski JQ, Lee VM, Balin BJ, Ding XS, Greenberg J, Morrison D, Reivich M, Grossman M. Cognitive, neuroimaging, and pathological studies in a patient with Pick's disease. **Ann Neurol.** 1998 Feb;43(2):259-65

Mawal-Dewan, M., Schmidt, M.L., Balin B.J., Perl D.P., Lee, M.-Y.L. and Trojanowski, J.Q.: Identification of phosphorylated sites in PHF-tau from patients with Guam Amyotrophic lateral sclerosis/Parkinsonism-Dementia Complex. **J. Neuropathol. Exper. Neurol. 55**:1051-1059, 1996.

Balin BJ, Lee VM. Individual neurofilament subunits reassembled in vitro exhibit unique biochemical, morphological and immunological properties. **Brain Res.** 1991 Aug 16;556(2):196-208.

Balin BJ, Clark EA, Trojanowski JQ, Lee VM. Neurofilament reassembly in vitro: biochemical, morphological and immuno-electron microscopic studies employing monoclonal antibodies to defined epitopes. **Brain Res.** 1991 Aug 16;556(2):181-95.

Mulligan L, Balin BJ, Lee VM, Ip W. Antibody labeling of bovine neurofilaments: implications on the structure of neurofilament sidearms. **J Struct Biol.** 1991 Apr;106(2):145-60.

Balin BJ, Broadwell RD. Transcytosis of protein through the mammalian cerebral epithelium and endothelium. I. Choroid plexus and the blood-cerebrospinal fluid barrier. **J Neurocytol.** 1988 Dec;17(6):809-26.

Broadwell RD, Balin BJ, Salcman M. Transcytotic pathway for blood-borne protein through the blood-brain barrier.
Proc Natl Acad Sci U S A. 1988 Jan;85(2):632-6.

Balin BJ, Broadwell RD, Salcman M. Tubular profiles do not form transendothelial channels through the blood-brain barrier.
J Neurocytol. 1987 Dec;16(6):721-35. Erratum in: J Neurocytol 1988 Jun;17(3):416.

Broadwell RD, Charlton HM, Balin BJ, Salcman M. Angioarchitecture of the CNS, pituitary gland, and intracerebral grafts revealed with peroxidase cytochemistry.
J Comp Neurol. 1987 Jun 1;260(1):47-62.

Broadwell, R.D., Balin, B.J. and Cataldo, A.M.: Fine structure and cytochemistry of the median eminence. In: Gross, P.M., (ed.): **Circumventricular Organs and Body Fluids.** Boca Raton, Fla.: **CRC Press,** 1987.

Balin BJ, Broadwell RD, Salcman M, el-Kalliny M. Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, and squirrel monkey.
J Comp Neurol. 1986 Sep 8;251(2):260-80.

Broadwell RD, Balin BJ. Endocytic and exocytic pathways of the neuronal secretory process and trans-synaptic transfer of wheat germ agglutinin-horseradish peroxidase in vivo.
J Comp Neurol. 1985 Dec 22;242(4):632-50.

Broadwell RD, Cataldo AM, Balin BJ. Further studies of the secretory process in hypothalamo-neurohypophysial neurons: an analysis using immunocytochemistry, wheat germ agglutinin-peroxidase, and native peroxidase.
J Comp Neurol. 1984 Sep 10;228(2):155-67.

Broadwell RD, Balin BJ, Salcman M, Kaplan RS. Brain-blood barrier? Yes and no.
Proc Natl Acad Sci U S A. 1983 Dec;80(23):7352-6.

Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias of Late Life

WORK GROUP ON ALZHEIMER'S DISEASE AND RELATED DEMENTIAS
Peter Rabins, M.D., M.P.H., Chair
Deborah Blacker, M.D., Sc.D. (Consultant)
Walter Bland, M.D.
Lory Bright-Long, M.D.
Eugene Cohen, M.D.
Ira Katz, M.D.
Barry Rovner, M.D.
Lon Schneider, M.D.

STEERING COMMITTEE ON PRACTICE GUIDELINES
John S. McIntyre, M.D., Chair
Sara C. Charles, M.D., Vice-Chair
Deborah A. Zarin, M.D., Director, Practice Guideline Program
Harold Alan Pincus, M.D., Director, Office of Research
Kenneth Altshuler, M.D.
William Ayres, M.D.
Thomas Bittker, M.D.
Paula Clayton, M.D.
Ian Cook, M.D.
Helen Egger, M.D.
Steven Jaffe, M.D.
Sheldon Miller, M.D.
Louis Alan Moench, M.D.
Roger Peele, M.D.
Bruce Phariss, M.D.
Mary Carol Shemo, M.D.
Susan Stabinsky, M.D.
Stuart W. Twemlow, M.D.

CONSULTANTS AND LIAISONS
William Clayton, M.D. (Liaison)
Laurie Flynn (Consultant)
Marcia Goin, M.D. (Liaison)
Marion Goldstein, M.D. (Liaison)
Richard Kent Harding, M.D. (Consultant)
James Hooper, M.D. (Consultant)
Maria Lymberis, M.D. (Liaison)
Grayson Norquist, M.D. (Consultant)
Sydney Weissman, M.D. (Liaison)
Joel Yager, M.D. (Consultant)
Al Herzog, M.D. (Area I)
James Nininger, M.D. (Area II)
John Urbaitis, M.D. (Area III)

Philip Margolis, M.D. (Area IV)
Allen Kayser, M.D. (Area V)
Lawrence Lurie, M.D. (Area VI)
R. Dale Walker, M.D. (Area VII)

STAFF
Leslie Selgle, Project Manager

Table of Contents

IV. Development of a Treatment Plan

A. Mildly Impaired Patients

At the early stages of a dementing illness, patients and their families are often dealing with recognition of the illness and associated limitations, and they may appreciate suggestions for how to cope with these limitations (e.g., making lists, using a calendar). It may be helpful to identify specific impairments and highlight remaining abilities. Families and patients may also suffer from a sense of loss and from a perceived stigma associated with the illness. Mildly impaired patients should also be advised about the risk of driving. Although there is no consensus on this issue, a review of the data coupled with a concern for the safety of the patient and others suggest that patients with mild impairment should be urged to stop driving or to limit their driving to familiar routes and less challenging situations (e.g., good road conditions, low speeds, spouse or other navigator in the car). At this stage of the illness, the patient should also be advised to draw up a power of attorney for medical and financial decision making, an advance directive, and/or a living will. Patients may also wish to revise their wills and to make the necessary financial arrangements to plan for long-term care. Caregivers should be made aware of the availability of support groups and social agencies.

Patients with Alzheimer's disease seen in the early stages may be offered a trial of tacrine or donepezil for cognitive impairment. Although available data are limited to moderately impaired patients, it is possible that vitamin E might also delay progression of Alzheimer's disease in patients with mild impairment. Thus, physicians might consider vitamin E alone or possibly in combination with a cholinesterase inhibitor at this stage. Selegiline, which also delayed progression in moderately impaired patients, might also be considered, although vitamin E may be preferable because of its more favorable side effect profile and lack of drug interactions. Mildly impaired patients might also be interested in referrals to local research centers for participation in clinical trials of experimental agents for the treatment of Alzheimer's disease. Additional information regarding such trials may be obtained from the local or national chapter of the Alzheimer's Association or from the National Institute on Aging.

Mildly impaired patients also deserve a careful evaluation for depressed mood or major depression, which suggests the need for pharmacologic intervention, as reviewed in section III.D.4.b. Patients with moderate to severe major depression who do not respond to or cannot tolerate antidepressant medications should be considered for ECT. Particularly-but not only-if they are depressed, mildly impaired patients should also be carefully assessed for suicidality.

B. Moderately Impaired Patients

As patients become more impaired, they are likely to require more supervision to remain safe. Families should be advised regarding the possibility of accidents due to forgetfulness (e.g., fires while cooking), of difficulties coping with household emergencies, and of the possibility of wandering. Family members should be advised to determine whether the patient is handling finances appropriately and to consider taking

over the paying of bills and other responsibilities. At this stage of the disease, patients should be strongly urged not to drive, and families should be urged to undertake measures (such as taking away the car keys) to prevent patients from driving.

As patients' dependency increases, caregivers may begin to feel more burdened. A referral for some form of respite care (e.g., home health aid, day care, or brief nursing home stay) may be helpful. At this stage, families should begin to consider and plan for additional support at home or possible transfer to a long-term care facility.

Treatment for cognitive symptoms should also be considered at this stage. For patients with Alzheimer's disease, currently available data suggest that a trial of tacrine or donepezil is the intervention most likely to lead to improvement in cognitive function. In addition, vitamin E or selegiline, which have been shown to delay progression in Alzheimer's disease patients with moderate impairment, may be offered to patients at this stage. Vitamin E appears preferable because of its low toxicity and lack of drug interactions. It may be appropriate to offer vitamin E in combination with a cholinesterase inhibitor.

Delusions and hallucinations often develop in moderately impaired patients. The patient and family may be troubled and fearful about these symptoms, and it may be helpful to reassure them that the symptoms are part of the illness and are often treatable. If these symptoms cause no distress to the patient and are unaccompanied by agitation or combativeness, they are probably best treated with reassurance and distraction. If they do cause distress or are associated with behavior that may place the patient or others at risk, they should be treated with low doses of antipsychotic medications. If a patient is agitated or combative in the absence of psychosis, treatment with an antipsychotic medication has the most support in the literature, but carbamazepine, valproate, trazodone, buspirone, or possibly an SSRI may be used in a careful therapeutic trial. If behavioral symptoms are time limited, a benzodiazepine may also prove useful. Depression often remains part of the picture at this stage and should be treated vigorously.

C. Severely And Profoundly Impaired Patients

At this stage of the illness, patients are severely incapacitated and are almost completely dependent on others for help with basic functions, such as dressing, bathing, and feeding. Families are often struggling with a combined sense of burden and loss and may benefit from a frank exploration of these feelings and any associated resentment or feelings of guilt. They may also need encouragement to get additional help at home or to consider nursing home placement.

There are no data available to guide decisions about the use of cognition-enhancing medications for the severely impaired: use of these medications may be continued, or a medication-free trial may be used to assess whether the medication is still providing a benefit.

Similarly, there are no data available about whether vitamin E or selegiline retards the progression at this stage, and, for patients who reach this stage of illness already taking one of these agents, even a medication-free interval may not clarify the picture, since the

References

1. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004;363:2105-2115.

2. Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. Int J Geriatr Psychiatry. 2004;19:624-633.

3. Ritchie CW, Ames D, Clayton T, Lai R. Meta-analysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease. Am J Geriatr Psychiatry. 2004;12:358-369.

4. Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology. 2001;57:481-488.